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(71) Applicant *(for all designated States except US)*: **NICAST LTD.** [IL/IL]; Brosh Building - Global Park, 2 Yodfat Street, North Industry Zone, 71291 Lod (IL).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **DUBSON, Alexander** [IL/IL]; 36A Shapira Street, 49491 Petach-Tikva (IL).

(74) Agent: **G.E. EHRLICH** (1995) **LTD.**; 11 Menachem Begin Street, 52 521 Ramat Gan (IL).

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(54) **Title:** METHOD AND SYSTEM FOR MANUFACTURING ELECTROSPUN STRUCTURES

(57) **Abstract:** A system for manufacturing an electrospun structure, is disclosed. The system comprises an electrospinning system having a precipitation electrode, and a dispenser being at a first electric potential relative to the precipitation electrode and capable of dispensing a liquefied polymer to produce polymer fibers precipitating on the precipitation electrode, thereby to form the electrospun structure thereupon. The system further comprises a subsidiary electrode system, being at a second potential relative to the precipitation electrode and configured to shape an electric field formed between the precipitation electrode and the dispenser. The system also comprises a compartment, encapsulating the electrospinning system and the subsidiary electrode system, for keeping a clean environment within the compartment.

METHOD AND SYSTEM FOR MANUFACTURING ELECTROSPUN STRUCTURES

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to electrospinning and more particularly to a method and system for manufacturing electrospun structures.

Polymer fiber shells such as tubular shaped products are used in the medical industry for various utilities including esophageal grafts, vascular grafts, stent coats and like.

Numerous methods for manufacturing polymer fiber shells suitable for medical applications are known in the art, including, for example, various injection molding methods, mandrel assisted extrusion or formation and various weaving techniques.

Production of polymer fiber shells suitable for use as vascular grafts is particularly difficult. In vascular grafts, tissue ingrowth and cell endothelization is typically enhanced with increased in grafts exhibiting increased porosity. However, increasing the porosity of vascular grafts leads to a considerable reduction of the mechanical and tensile strength of the graft, and as a consequence to a reduction in the functionality thereof.

Electrospinning has been used for generating various products for medical applications, e.g., wound dressings, prosthetic devices and vascular grafts as well as for industrial use, e.g., electrolytic cell diaphragms, battery separators and fuel cell components. It has already been proposed to produce by electrospinning products having the appearance of shells. For example, U.S. Patent No. 4,323,525 discloses a method of preparing a tubular product by electrostatically spinning a fiber forming material and collecting the resulting spun fibers on a rotating mandrel. U.S. Patent No. 4,552,707 discloses a varying rotation rate mandrel which controls the "anisotropy extent" of fiber orientation of the final product. Additional examples of tubular shaped products and a like are disclosed, e.g., in U.S. Patent Nos. 4,043,331, 4,127,706, 4,143,196, 4,223,101, 4,230,650 and 4,345,414.

The process of electrospinning creates a fine stream or jet of liquid that upon proper evaporation yields a non-woven fiber structure. The fine stream of liquid is produced by pulling a small amount of a liquefied polymer (either polymer dissolved in solvent (polymer solution) or melted polymer) through space using electrical forces.

The produced fibers are then collected on a suitably located precipitation device, such as a mandrel to form tubular structures. In the case of a melted polymer which is normally solid at room temperature, the hardening procedure may be mere cooling, however other procedures such as chemical hardening or evaporation of solvent may also be employed.

In electrospinning, an electric field with high intensity *(i.e.,* having large magnitude per unit volume) may results in a corona discharge near the precipitation device, fibers recharge and consequently prevents fibers from being collected by the precipitation device. The filed lines density of an electric field is determined inter alia by the geometry of the precipitation device; in particular, sharp edges on the precipitation device dramatically increase the effect of corona discharge.

In addition, due to the effect of electric dipole rotation along the electric field maximal strength vector in the vicinity of the mandrel, products with at least a section with a small radius of curvature are coated coaxially by the fibers. Such structural fiber formation considerably reduces the radial tensile strength of a spun product, which, in the case of vascular grafts, is necessary for withstanding pressures generated by blood flow.

Various electrospinning based manufacturing methods for generating vascular grafts are known in the prior art, see, for example, U.S. Patent Nos. 4,044,404, 4,323,525, 4,738,740, 4,743,252, and 5,575,818. However, such methods suffer from the above inherent limitations which limit the use thereof when generating intricate profile fiber shells.

International Publication No. WO 02/049678 discloses an electrospinning apparatus designed for manufacturing tubular fiber shell of small diameters. The apparatus includes a precipitation electrode, a dispenser and a subsidiary electrode, where both the dispenser and the subsidiary electrode are kept at potential differences from the precipitation electrode. The subsidiary electrode reduces non uniformities in the electric field generated the precipitation electrode and the dispenser. In use, a liquefied polymer is charged and dispensed by the dispenser under the influence of the electric field, resulting in polymer fabrication. The polymer fibers sediment on the precipitation electrode, which rotates to form a nonwoven tubular structure thereon.

Electrospinning remains, however, a very complicated multi-factor process demanding high-precision technological conditions at all manufacturing stages.

Besides, fabrication of certain products demands for the application of specific spinning techniques and connection of differing layers.

Furthermore, the removal of the electrospun product from the precipitation electrode is known to be a very cumbersome operation due to the adherence of the fibers to the precipitation electrode. The removal process oftentimes restricts the fabrication process efficiency as well as the quality of the final produce. For example, when the electrospun product is a vascular prosthesis, the shear force necessary for removing the electrospun product from the precipitation electrode exceeds its tensile strength, resulting in severe damage to the product. One solution to this problem involves the coating of the precipitation electrode by cloth or foil. However, it is difficult to remove these substances from the inner surface of the electrospun product. Additionally, the use of these substrates reduces the ability to accurately control the size and shape of the products.

The present invention provides solutions to the problems associated with prior art electrospinning apparatus.

SUMMARY OF THE INVENTION

According to one aspect of the present invention there is provided a system for manufacturing an electrospun structure, comprising: (a) an electrospinning system having a precipitation electrode, and a dispenser being at a first electric potential relative to the precipitation electrode and capable of dispensing a liquefied polymer to produce polymer fibers precipitating on the precipitation electrode, thereby to form the electrospun structure thereupon; (b) a subsidiary electrode system, being at a second potential relative to the precipitation electrode and configured to shape an electric field formed between the precipitation electrode and the dispenser; and (c) a compartment, encapsulating the electrospinning system and the subsidiary electrode system, for keeping a clean environment of class 1000 or cleaner within the compartment.

According to another aspect of the present invention there is provided a method of manufacturing an electrospun structure, comprising providing at least one liquefied polymer, using The system, method or electrospun structure of claim 1 so as to form the electrospun structure on the precipitation electrode and removing the electrospun structure from the precipitation electrode.

According to further features in preferred embodiments of the invention described below, the removal of the electrospun structure from the precipitation electrode comprises irradiating the precipitation electrode including the electrospun structure by ultrasound radiation.

According to still further features in the described preferred embodiments the removal of the electrospun structure from the precipitation electrode further comprises subjecting the precipitation electrode including the electrospun structure to at least one substantially abrupt temperature change.

According to yet another aspect of the present invention there is provided a method of removing an electrospun structure from a precipitation electrode, comprising subjecting the precipitation electrode including the electrospun structure to at least one substantially abrupt temperature change, while irradiating the precipitation electrode including the electrospun structure by ultrasound radiation.

According to further features in preferred embodiments of the invention described below, the precipitation electrode including the electrospun structure are immersed in an ultrasonic bath of low temperature for a first predetermined period, and in an ultrasonic bath of high temperature for a second predetermined period.

According to still further features in the described preferred embodiments the further comprises a data processor communicating with the electrospinning system and being supplemented by an algorithm, for controlling the operation of the electrospinning system.

According to still further features in the described preferred embodiments the further comprises a thickness meter for real-time monitoring of the thickness of a wall of the electrospun structure, the thickness meter communicating with the data processor.

According to still further features in the described preferred embodiments the data processor is configured to cease the operation of the electrospinning system when the thickness equals or above a predetermined threshold.

According to still further features in the described preferred embodiments the further comprises an illumination system for illuminating the polymer fibers while moving from the dispenser to the precipitation electrode.

According to still further features in the described preferred embodiments the dispenser is operable to select the liquefied polymer from at least two different liquefied polymers.

According to still further features in the described preferred embodiments the electrospun structure comprises a plurality of layers and further wherein the data processor is configured to instruct the dispenser to select the liquefied polymer from the at least two different liquefied polymers for each layer of the plurality of layers.

According to still further features in the described preferred embodiments the dispenser comprises a plurality of atomizers, respectively mounted on a plurality of manifolds devoid of fluid communication thereamongst, each manifold of the plurality of manifolds comprises a different liquefied polymer and being designed and constructed to supply the different liquefied polymer to a respective atomizer. According to still further features in the described preferred embodiments each atomizer comprises a plurality of spinnerets.

According to still further features in the described preferred embodiments the plurality of manifolds are mounted on a turret, operable to assume a plurality of orientations, such that at each orientation of the plurality of orientations, a different atomizer is directed to the precipitation electrode.

According to still further features in the described preferred embodiments the system further comprises at least one pressure sensor operatively associated with the dispenser and being in communication with the data processor, for measuring the hydrostatic pressure of the liquefied polymer in the dispenser.

According to still further features in the described preferred embodiments the system further comprises at least one temperature sensor operatively associated with the dispenser and being in communication with the data processor, for measuring the temperature of the liquefied polymer in the dispenser.

According to still further features in the described preferred embodiments the further comprises a pump system controllable by the data processor, wherein the data processor is configured to stabilize the hydrostatic pressure of the liquefied polymer in the dispenser by controlling the pump system.

According to still further features in the described preferred embodiments at least one of the dispenser and the precipitation electrode is operable to rotate such that

a relative rotary motion is established between the dispenser and the precipitation electrode.

According to still further features in the described preferred embodiments at least one of the dispenser and the precipitation electrode is operable to move such that a relative linear motion is established between the dispenser and the precipitation electrode.

According to still further features in the described preferred embodiments the data processor is configured to vary at least one of the relative rotary motion and the relative linear motion so as to control precipitation rate of the polymer fibers on the precipitation electrode.

According to still further features in the described preferred embodiments the precipitation electrode comprises at least one rotating mandrel.

According to still further features in the described preferred embodiments the rotating mandrel is operatively associated with a motor controllable by the data processor.

According to still further features in the described preferred embodiments the subsidiary electrode system comprises at least one cylindrical electrode.

According to still further features in the described preferred embodiments the subsidiary electrode system comprises at least one planar electrode.

According to still further features in the described preferred embodiments the further comprises a first position adjustment mechanism for varying the position of the subsidiary electrode system relative to the precipitation electrode. According to still further features in the described preferred embodiments the further comprises a second position adjustment mechanism for varying the position of the dispenser relative to the precipitation electrode. According to still further features in the described preferred embodiments the further comprises an angular adjustment mechanism for varying the relative angle between the dispenser and the precipitation electrode.

The present invention successfully addresses the shortcomings of the presently known configurations by providing a method and system, and, more preferably an automated method and system for manufacturing electrospun structures

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those

described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of the preferred embodiments of the present invention only, and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the invention. In this regard, no attempt is made to show structural details of the invention in more detail than is necessary for a fundamental understanding of the invention, the description taken with the drawings making apparent to those skilled in the art how the several forms of the invention may be embodied in practice.

In the drawings:

FIGs. la-d are schematic illustrations of a isometric view (Figure la), front view (Figure lb), top view (Figure lc) and side view (Figure ld) of a system for manufacturing an electrospun structure, in accordance with various exemplary embodiments of the present invention;

FIGs. 2a-b are schematic illustrations of subsidiary electrodes and position adjustment mechanisms, in accordance with various exemplary embodiments of the present invention;

FIG. 3 is an enlarged schematic illustration of a mechanism for establishing a rotary motion of a precipitation electrode, in accordance with various exemplary embodiments of the present invention;

FIGs. 4a-b are enlarged schematic illustrations of a mechanism for establishing the linear motion of a dispenser, in accordance with various exemplary embodiments of the present invention;

FIGs. 5a-b are enlarged schematic illustrations of an isometric view (Figure 5a) and a side cross sectional view (Figure 5b) of the dispenser, in accordance with various exemplary embodiments of the present invention; and

FIG. 6 is a schematic illustration of a two-layered tubular electrospun structure, in accordance with various exemplary embodiments of the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is of a method and system which can be used to produce electrospun structures. Specifically, the present invention can be used in automatic manufacture mass production of electrospun structures. In various exemplary embodiments of the invention the method and system are automated and can be controlled by a data processor. The present invention is further of an electrospun structures manufactured by the method.

The principles and operation of a system and method according to the present invention may be better understood with reference to the drawings and accompanying descriptions.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details of construction and the arrangement of the components set forth in the following description or illustrated in the drawings. The invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

Referring now to the drawings, Figure la-d illustrate a system 10 for manufacturing an electrospun structure. Figure Ia is an isometric view, in which three viewpoints A, B and C are marked, Figure Ib is a front view, as seen from viewpoint A, Figure Ic is a top view as seen from viewpoint B and Figure Id is a side view as seen from viewpoint C.

In its simplest configuration, System 10 comprises an electrospinning system 20 having a precipitation electrode 22, and a dispenser 24, positioned at a predetermined distance from a precipitation electrode 22 and being kept at a first potential relative to precipitation electrode 22.

Typically, dispenser 24 is connected by line 26 to a source 25 of high voltage, preferably of negative polarity, while precipitation electrode 22 is grounded. Alternatively, precipitation electrode 22 can be connected to a high voltage source of positive polarity while dispenser 24 can be grounded. In any case, the potential

difference between dispenser 24 and precipitation electrode 22 is from about 10 kV to about 100 kV, typically about 60 kV. The potential difference between dispenser 24 and precipitation electrode 22 generate an electric field therebetween.

As used herein the term "about" refers to ± 10 %.

Dispenser 24 serves for dispensing a liquefied polymer in the electric field to produce polymer fibers precipitating on electrode 22. Precipitation electrode 22 serves for forming the electrospun structure thereupon. Precipitation electrode 22 is typically manufactured in accordance with the geometrical properties of the final product which is to be fabricated. In various exemplary embodiments of the invention the electrospun structure has a tubular shape and electrode 22 is in a form of a rotating mandrel. Electrode 22 can be made of, for example, stainless steel.

System 10 further comprises a subsidiary electrode system **30,** which is preferably at a second potential relative to precipitation electrode 22 and configured to shape the aforementioned electric field. Typically, electrode system **30** is connected to source 25 by line 34 and a circuitry 32 which alters (typically reduce) the output voltage of 25 to the desired level. A typical potential difference between electrode 22 and electrode system 30 is from about 10 kV to about 100 kV, typically about 50 kV.

Electrode system **30** may comprise a plurality of electrodes in any arrangement. The size, shape, position and number of electrodes in system **30** is preferably selected so as to maximize the coating precipitation factor, while minimizing the effect of corona discharge in the area of precipitation electrode 22 and/or so as to provide for controlled fiber orientation upon deposition.

In the exemplified configuration shown in Figures la-d, which is not to be considered as limiting, system **30** comprises three cylindrical electrodes, designated **30a, 30b** and **30c,** where electrode **30a** is of larger diameter and is positioned behind precipitation electrode 22, while electrodes **30b** and **30c** are of smaller diameter and poisoned above and below electrodes electrode 22. Electrodes 30a, **30b** and **30c** are better seen in Figures 2a (electrode **30a)** and 2b (electrodes **30b** and **30c).**

Subsidiary electrode system **30** controls the direction and magnitude of the electric field between precipitation electrode 22 and dispenser 24 and as such, can be used to control the orientation of polymer fibers precipitated on electrode 22. In some embodiments, subsidiary electrode system **30** serves as a supplementary screening electrode. Generally, the use of screening results in decreasing the coating

precipitation factor, which is particularly important upon cylindrical precipitation electrodes having at least a section of small radii of curvature.

Electrode shapes which can be used in the present embodiments include, but are not limited to, a plane, a cylinder, a torus a rod, a knife, an arc or a ring.

Specifically, a cylindrical or planar subsidiary electrode enables manufacturing intricate-profile products being at least partially with small (from about 0.025 millimeters to about 5 millimeters) radius of curvature. Such subsidiary electrodes are also useful for achieving random or circumferential alignment of the fibers onto precipitation electrode 22.

The ability to control fiber orientation is important when fabricating vascular grafts in which a high radial strength and elasticity is important. It will be appreciated that a polar oriented structure can generally be obtained also by wet spinning methods, however in wet spinning methods the fibers are thicker than those used by electrospinning by at least an order of magnitude.

Control over fiber orientation is also advantageous when fabricating composite polymer fiber shells which are manufactured by sequential deposition of several different fiber materials.

Subsidiary electrodes of small radius of curvature *(e.g.,* electrodes **30b** and **30c),** can be used to introduce distortion the electric field in an area adjacent to precipitation electrode 22. For maximum effect the diameter of subsidiary electrode 26 must be considerably smaller than that of precipitation electrode 22, yet large enough to avoid generation of a significant corona discharge.

According to a preferred embodiment of the present invention system 10 comprises a position adjustment mechanism 27 for varying the position of subsidiary electrode system 26 relative to precipitation electrode 22. Such design further facilitates the ability to control the electric field vector (intensity and direction) near electrode 22.

System 10 further comprises a compartment 12 (for clarity shown only in Figure Ia), encapsulating electrospinning system 20 and subsidiary electrode system **30.** Preferably, but not obligatorily, compartment 12 also encapsulates source 25, and circuitry 32, including the connection lines. Compartment 12 is preferably made of a material being transmissive hi the visual range,

Compartment 12 serves for keeping a clean environment therein. According to a preferred embodiment of the present invention the clean environment is of class 1000 *(i.e.,* less than one thousands particles larger than 0.5 microns in each cubic foot of space) or cleaner. More preferably the clean environment is of class 100 *(i.e.,* less than one thousand particles larger than 0.5 microns in each cubic foot of air space).

More specifically, compartment 12 serves as a climate chamber which besides the clean environment, maintains therein predetermined levels of other environmental conditions such as temperature and humidity.

Thus, according to a preferred embodiment of the present invention the temperature with compartment 12 is kept at a predetermined constant level within an accuracy of ± 1 °C, more preferably ±0.5 °C even more preferably ±0.2 °C, so as to control and maintain the desired evaporation rate during the electrospinning process. Maintenance of accurate temperature within compartment 12 is advantageous because the thickness of the produced polymer fibers and the porosity of the electrospun structure, depends, *inter alia,* on the evaporation rate of solvent from the polymer jets emerge from dispenser 24. Preferred temperatures for the operation are from about 22 °C to about 40 ^{0}C.

Additionally, the humidity within compartment 12 is maintained at a predetermined level to an accuracy of 5 % more preferably 3 % even more preferably 1 %. Maintenance of accurate temperature within compartment 12 is useful for preventing or reducing formation of volume charge. Preferred humidity level, in relative value (the weight or pressure of moisture relative to the maximal weight or pressure of moisture for a given temperature) is about 40 %.

Dispenser 24 and/or precipitation electrode 22 preferably rotates such that a relative rotary motion is established between dispenser 24 and electrode 22. Similarly, Dispenser 24 and/or electrode 22 preferably moves such that a relative linear motion is established between dispenser 24 and electrode 22. In the exemplified configuration shown in Figures la-d, precipitation electrode rotates without performing a linear motion, while dispenser 24 performs a linear motion without performing a rotary motion. However, this need not necessarily be the case, since, for some applications, it may be desired to rotate dispenser 24 about a longitudinal axis 21 of electrode 22 and/or to establish a linear motion of electrode 22 along its longitudinal axis.

When electrode 22 rotates about its axis, it can be,.for example, in a form of a rotating mandrel mounted on supports 38 via clamps 36, which are preferably designed to facilitate the disengagement of electrode 22 from supports 38, for example, for the purpose of removing the electrospun structure from the mandrel. Clamps 36 preferably have small transversal cross section, so as to minimize or eliminate distortions of the electric field. According to a preferred embodiment of the present invention supports 38 are made of a dielectric material and are located in an electric shadow created by electrode 22. The rotation of the electrode 22 can be effected by any mechanism, such as, but not limited to, an electrical motor, an electromagnetic motor, a pneumatic motor, a hydraulic motor, a mechanical gear and the like.

Figure 3 is an enlarged schematic illustration of the mechanism which establishes the rotary motion of electrode 22, according to a preferred embodiment of the present invention. Electrode 22 is mounted on a bearing member 48 engaging a belt 46 thereby. An electric motor 40 rotates a shaft 42 which transmits the rotary motion via a set of wheels 44 and belt 46 to bearing member 48 to thereby rotate electrode 22. A typical angular velocity of electrode 22 is from about 0.1 to about 10 radians per second.

Figure 4a-b are enlarged schematic illustrations of the mechanism which establishes the linear motion of dispenser 24, according to a preferred embodiment of the present invention. Dispenser 24 is mounted on convey 54 being oriented at a predetermined angle to electrode 22 (not shown in Figure 3). An electric motor 58 generates a rotary motion which is transformed by a gear 60 to a linear motion of convey 54 thereby also of dispenser 24. A typical linear velocity of dispenser 24 is from about 0.001 to about 0.1 meters per second.

Convey 54 can be mounted on position adjustment mechanism 64 so as to allow adjustment of the distance between dispenser 24 and electrode 22. Mechanism 64 can be in a form of, for example, one or more parallel tracks 64 onto which convey 54 is mounted.

The relative angle between convey 54 (hence also of dispenser 24) and electrode 22 can be varied by means of an angular adjustment mechanism 62, which can be in a form of, for example, a rotatable member having a groove which facilitates the mounting of convey 54 on track 64 at a plurality of angles. According to a

preferred embodiment of the present invention the relative angle between convey 54 and electrode 22 can vary from about 0° to about 30°.

Referring again to Figure la, system 10 preferably comprises a data processor 50 supplemented by an algorithm for controlling the operation of electrospinning system 20. Data processor 50 can communicate with system 20 directly or through a control unit 51 located within compartment 12. The communication can be via communication line 52 or, more preferably, via wireless communication so as to preserve to clean environment in compartment 12. Preferably, but not obligatorily, processor 50 also communicates *(e.g.,* through control unit 51 and communication line 53) with source 25 for controlling the aforementioned potential differences and for automatically activating and deactivating system 10. According to a preferred embodiment of the present invention processor 50 is configured (e.g., by a suitable computer program) to vary the relative rotary motion and/or relative linear motion between dispenser 24 and electrode 22. For example, when electrode 22 rotates by means of electric motor 40, the power supplied to motor 40, hence the angular velocity of electrode 22 is controlled by processor 50. Similarly, when dispenser 24 moves along convey 54 by means of electric motor 58, the power supplied to motor 58, hence the linear velocity of dispenser 24 is controlled by processor 50.

As will be appreciated by one ordinarily skilled in the art, different angular and/or linear relative velocities can result in different precipitation rates of polymer fibers on electrode 22. Thus, the computerized control on the motions can be used to select the desired precipitation rate, hence also the desired wall thickness of the electrospun structure.

Additionally, processor 50 can signal the mechanism for establishing the linear and/or angular motions of dispenser 24 and/or electrode 22 to change the corresponding velocities, at a given instant or instances of the process. This embodiment is particularly useful when manufacturing multilayer electrospun structures. Thus, by selecting different motion characteristics of dispenser 24 and/or electrode 22 for different layers, the electrospinning process for each layer is at a different precipitation rate, resulting in a different density of fibers on the formed layer. Since the porosity of the layer depends on the density of fiber, such process can be used for manufacturing multilayer electrospun structures in which the layers have

predetermined and different porosities. Additionally, each layer can have a different wall thickness, which can also be controlled as further detailed above.

For example, when the electrospun structure is a vascular prosthesis, it can be made of two or more layer, whereby the inner layer can be substantially smooth (with small porosity) and the outer layer has a larger porosity. Thus the inner layer can serve as a sealing layer to prevent bleeding, and to ensure antithrombogenic properties and efficient endothelization. A typical thickness of such first layer 12 is from about 40 μm to about 80 μm. The outer layer provides the vascular prosthesis with the requisite mechanical properties such as high compliance and high breaking strength. The thickness of the second layer is preferably larger, from about 50 μm to about 1000 μm. In addition, the larger porosity of the outer layer promotes ingrowth of surrounding tissues, which is extremely important for fast integration and long-term patency of the vascular prosthesis.

With reference to Figures la-d, according to a preferred embodiment of the present invention electrospinning system 20 comprises a pump system 14 which feeds dispenser 24 by one or more liquefied polymers which can be melted or dissolved. Pump system 14 is preferably in communication with data processor 50, either directly or by control unit 51. The communication with pump system 14 allows processor 50 to control the feeding rate of the liquefied polymer(s) into dispenser 24.

Pump system 14 can comprises one or more syringes 16, which can be made of, for example, stainless-steel. According to a preferred embodiment of the present invention the pump system has a nominal measuring accuracy of ± 0.1 milliliter per hour, more preferably ± 0.5 milliliter per hour, even more preferably ± 0.1 milliliter per hour, so as to preserve preset accuracy and achieve high repeatability of electrospinning results.

A fluid communication between pump system 14 and dispenser 24 is preferably established by one or more pipes 19 aligned within one or more tubes 18. Tubes 18 can also contain electrical communication lines for transmitting information to dispenser 24. Tubes 18 and pipes 19 are preferably made flexible so as to allow dispenser 24 to remain in fluid and/or electrical communication while moving along convey 54. Tubes 18 and pipes 19 can be made, for example, from poly-tetrafluorethylene which is known to be a non-deformable material under the typical working strains of system 10.

According to a preferred embodiment of the present invention dispenser can select the liquefied polymer from two or more different liquefied polymers. This embodiment is particularly useful when the electrospun structure comprises a plurality of layers, whereby two layers may be formed from different type of polymer fibers. Thus, in various exemplary embodiments of the invention data processor 50 instructs dispenser 24 to reselect the liquefied polymer for each layer of the electrospun structure.

Reference is now made to Figures 5a-b, which are enlarged schematic illustrations of an isometric view (Figure 5a) and a side cross sectional view (Figure 5b) of dispenser 24, according to a preferred embodiment of the present invention. The cross sectional view is along the cut S_1-S_2 appearing in Figures 5a-b. One skilled in the art will recognize that several components of dispenser 24 have been omitted from Figure 5b for clarity of presentation.

Hence, according to the presently preferred embodiment of the invention dispenser 24 comprises a plurality of atomizers 72, respectively mounted on a plurality of manifolds 74. Each atomizer can be formed of one or more spinnerets 76. Shown in Figure 5a are two manifolds each carrying three spinnerets placed vertically in a row. A typical vertical distance between the spinnerets is about 20 mm, and the inner diameter of each spinneret is typically about 0.5 mm, which is suitable for a flow-rate of 0.1-10 milliliters of liquefied polymer per hour per spinneret. It is to be understood that this configuration is not to be considered as limiting and that any number of manifolds can be used with any number of spinnerets on each manifold.

Each manifold serves for supplying its respective atomizer (the three spinnerets in the present example) with a different liquefied polymer. Thus, manifolds 74 are preferably devoid of fluid communication thereamongst. As each manifold can supply a different type of polymer, the maximal possible types of polymers equals the number of manifolds. Each manifold's inner volume is preferably small so as to reduce losses of liquefied polymer and ensure stable hydrostatic pressure, in particular at the beginning of the process, when the possibility to pressure variations is higher. Manifolds 74 are connected to pump system 14 via pipes 19 (not shown see Figure lb).

Manifolds 74 are preferably mounted on a turret 76, which can assume a plurality of orientations, such that at each orientation a different atomizer is directed to

electrode 22. The relative orientation of the atomizers with respect to one another therefore depends on the number of atomizers employed. In the exemplified configuration of Figures 5a-b there are two atomizers hence the angular separation is preferably 180°. For three atomizers the orientation the angular separation is preferably 120°, for four atomizers 90° and so on.

The reorientation of turret 76 is preferably by a rotation mechanism 80, shown in Figure 5b, which rotates turret 76 about a pivot 78 to the desired orientation. The rotation is preferably generated by a miniature stepper motor 82 located with the body 84 of dispenser 24. Mechanical communication between motor 82 and pivot 78 is established by a transmission mechanism 96, which can be, for example, a pair of shafts 86a and 86b, respectively mounted on motor 82 and pivot 78 and a belt 88.

Processor 50 (not shown) can signal motor 82 to rotate turret 76 once a layer is completed so as to initiate the formation of a new layer. According to a preferred embodiment of the present invention, turret 76 performs a maneuver (switch from one predetermined orientation to another predetermined orientation) within less than one second, more preferably less than 0.5 seconds even more preferably less than 0.1 seconds. Thus, according to the presently preferred embodiment of the invention there a fast interchange between liquefied polymers can take place during the electrospinning process. Beside the advantage of continuity of the electrospinning process, the fast interchange between liquefied polymers enhances the adherence between successive layers, because the formation of the new layer begins before the polymer fibers of the previous layer are dried.

System 10 may further comprise one or more pressure sensors 68 (shown in Figures Ic, 4a and 5a) operatively associated with dispenser 24 for measuring the hydrostatic pressure of liquefied polymer in dispenser 24. Sensors 68 can be mounted on dispenser 24 as seen in Figures Ic and 4a. Preferably, sensors 68 are in communication with data processor 50 which can use the feedback from sensor 68 for displaying the hydrostatic pressure in dispenser 24 in real time. Additionally, processor can use the feedback to monitor and, if necessary, to transmit instructions to pump system 14 so as to stabilize the hydrostatic pressure in dispenser 24.

Processor 50 also monitors the temperature of the liquefied polymer and within confinement 12 so as to indicate the operator whether or not the process proceeds

under the appropriate conditions. The temperature monitoring can be achieved using a set of temperature sensors 70 transmitting feedback to processor 50.

In various exemplary embodiments of the invention system 10 comprises a thickness meter 90 for real-time monitoring of the wall thickness the electrospun structure. Thickness meter preferably signals data processor 50, which can be configured to automatically cease the operation electrospinning system 20 when the wall thickness equals or above a predetermined threshold, thickness meter 90 can be, for example, a laser meter which transmits laser radiation onto electrodes 22 and based on the reflected radiation, determine the thickness of the wall. The resolution of thickness meter 90 is preferably of about 100 μm, more preferably about 30 μm, most preferably about 10 μm.

System 10 can further comprise an illumination system 92 for illuminating the polymer fibers. Illumination system 92 preferably transmits focused light *(e.g.,* white light) on the path of the polymer fibers in their motion from dispenser 24 to precipitation electrode 22. The illumination provides visual control over the process.

In various exemplary embodiments of the invention, an electrospun structure, *e.g.,* such as the two layered electrospun tubular structure schematically illustrated in Figure 6, is manufactured as follows.

One or more liquefied polymers are provided and introduced into the pump system. Suitable liquefied polymers, include, without limitation, liquefied polyethyleneterephtalat and liquefied polyurethane, which are particularly useful when the electrospun structure is for medical use. Also contemplated, are other types of polymers, including, without limitation, polycarbonate based aliphatic polyurethanes, siloxane based aromatic polyurethanes, polydimethylsiloxane and other silicone rubbers, polyester, polyolefins, polymethyl- methacrylate, vinyl halide polymer and copolymers, polyvinyl aromatics, polyvinyl esters, polyamides, polyimides, polyethers, poly (L-lactic acid), poly (lactide-co-glycolide), polycaprolactone, polyphosphate ester, poly (hydroxy- butyrate), poly (glycolic acid), poly (DL-lactic acid), poly (amino acid), cyanocrylate, some copolymers and biomolecules such as DNA, silk, chitozan and cellulose and many others that can be dissolved in appropriate solvents and electrically spun.

The liquefied polymer(s) can also be mixed with one or more conductivity control agents or charge control agents for improving the interaction of the libers with the electric field.

The distance between the precipitation electrode and the subsidiary electrodes, the distance between the dispenser and the precipitation electrode, and the angle between the dispenser and the precipitation electrode are adjusted by the adjustments mechanism and recorded into the data processor.

System 10 is sealed by the compartment and the appropriate environmental conditions are established.

Parameters, such as, but not limited to, wall thickness, number of layer, angular and linear velocities, temperature, hydrostatic pressure, polymer viscosities, and the like, are recorded into the data processor. Also recorded are the types of polymers.

System 10 is activated and the liquefied polymer is extruded under the action of the hydrostatic pressure through the spinnerets. As soon as meniscus of the extruded liquefied polymer forms, a process of solvent evaporation or cooling starts, which is accompanied by the creation of capsules with a semi-rigid envelope or crust. Because the liquefied polymer possesses a certain degree of electrical conductivity, the capsules become charged by the electric field. Electric forces of repulsion within the capsules lead to a drastic increase in hydrostatic pressure. The semi-rigid envelopes are stretched, and a number of point micro-ruptures are formed on the surface of each envelope leading to spraying of ultra-thin jets of the liquefied polymer from the spinnerets.

Under the effect of a Coulomb force, the jets depart from the dispenser and travel towards the opposite polarity electrode, *i.e.*, the precipitation electrode. Moving with high velocity in the inter-electrode space, the jet cools or solvent therein evaporates, thus forming fibers which are collected on the surface of the precipitation electrode. A typical thickness of the fibers thus formed ranges between 50 nm and 50 μm.

Once a first layer is formed, the data processor signals the dispenser to reselect a different liquefied polymer (in embodiments in which different liquefied polymers are used for different layers), and the motion mechanisms to change the rotary and/or linear velocities (in embodiments in which different the layers have different wall

thicknesses and/or different porosities). The signaling of the data processor is preferably performed without ceasing the electrospinning process, such that the new layer is formed substantially immediately after the previous layer.

Once all the layers are formed, the compartment is opened and the precipitation electrode, including the electrospun structure formed thereupon is disengaged from the system. The electrospun structure is then removed from the precipitation electrode.

As stated in the Background section above, the removal of the electrospun product from the precipitation electrode is known to be a very cumbersome operation due to the adherence of the fibers to the precipitation electrode.

The present embodiments successfully provide solution to this problem.

Thus, according to a preferred embodiment of the present invention the precipitation electrode including the electrospun structure are irradiated by ultrasound radiation. It was found by the inventor of the present invention that ultrasound radiation facilitates the removal of the electrospun structure from the electrode. Additionally and more preferably, the precipitation electrode including the electrospun structure can also be subjected to at least one substantially abrupt temperature change. The abrupt temperature change can be applied by any suitable heat carrier, including, without limitation, a liquid bath. The removal process can also be controlled by the data processor. Specifically, the data processor can control the duration and level of the applied temperatures and/or the ultrasound radiation.

The process of removal can thus be performed in accordance with various exemplary embodiments of the invention as follows. The precipitation electrode including the electrospun structure is immersed in an ultrasonic bath of low temperature (about 0 °C) for a first predetermined period (about 1-10 minutes, more preferably 3-5 minutes). Subsequently, the precipitation electrode including the electrospun structure is immersed in another ultrasonic bath of high temperature (from about 40 ^{0}C to about 100 °C) for a second predetermined period (about 1-10 minutes, more preferably 3-5 minutes). In experiments performed by the present inventor it was found that the electrospun structure can then be removed from the precipitation electrode by an easy manual effort. A schematic illustration of a two layered electrospun structure is shown in Figure 6.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims. All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention.

WHAT IS CLAIMED IS:

1. A system for manufacturing an electrospun structure, comprising:

(a) an electrospinning system having a precipitation electrode, and a dispenser being at a first electric potential relative to said precipitation electrode and capable of dispensing a liquefied polymer to produce polymer fibers precipitating on said precipitation electrode, thereby to form the electrospun structure thereupon;

(b) a subsidiary electrode system, being at a second potential relative to said precipitation electrode and configured to shape an electric field formed between said precipitation electrode and said dispenser; and

(c) a compartment, encapsulating said electrospinning system and said subsidiary electrode system, for keeping a clean environment of class 1000 or cleaner within said compartment.

2. A method of manufacturing an electrospun structure, comprising providing at least one liquefied polymer, using The system, method or electrospun structure of claim 1 so as to form the electrospun structure on said precipitation electrode and removing said electrospun structure from said precipitation electrode.

3. The method of claim 2, wherein said removing said electrospun structure from said precipitation electrode comprises irradiating said precipitation electrode including said electrospun structure by ultrasound radiation.

4. The method of claim 2, wherein said removing said electrospun structure from said precipitation electrode further comprises subjecting said precipitation electrode including said electrospun structure to at least one substantially abrupt temperature change.

5. A method of removing an electrospun structure from a precipitation electrode, comprising subjecting said precipitation electrode including said electrospun structure to at least one substantially abrupt temperature change, while irradiating said precipitation electrode including said electrospun structure by ultrasound radiation.

6. The method of claim 2 or 5, wherein said subjecting said precipitation electrode including said electrospun structure to at least one substantially abrupt temperature change, comprises immersing said precipitation electrode including said electrospun structure in an ultrasonic bath of low temperature for a first predetermined period, and immersing said precipitation electrode including said electrospun structure in an ultrasonic bath of high temperature for a second predetermined period.

7. An electrospun structure obtained by executing the method of claim 2.

8. The system, method or electrospun structure of claim 1, 2 or 7, wherein the system further comprises a data processor communicating with said electrospirming system and being supplemented by an algorithm, for controlling the operation of said electrospirming system.

9. The system, method or electrospun structure of claim 8, wherein the system further comprises a thickness meter for real-time monitoring of the thickness of a wall of the electrospun structure, said thickness meter communicating with said data processor.

10. The system, method or electrospun structure of claim 9, wherein said data processor is configured to cease said operation of said electrospirming system when said thickness equals or above a predetermined threshold.

11. The system, method or electrospun structure of claim 1, 2 or 7, wherein the system further comprises an illumination system for illuminating said polymer fibers while moving from said dispenser to said precipitation electrode.

12. The system, method or electrospun structure of claim 8, wherein said dispenser is operable to select the liquefied polymer from at least two different liquefied polymers.

13. The system, method or electrospun structure of claim 12, wherein the electrospun structure comprises a plurality of layers and further wherein said data

processor is configured to instruct said dispenser to select the liquefied polymer from said at least two different liquefied polymers for each layer of said plurality of layers.

14. The system, method or electrospun structure of claim 13, wherein said dispenser comprises a plurality of atomizers, respectively mounted on a plurality of manifolds devoid of fluid communication thereamongst, each manifold of said plurality of manifolds comprises a different liquefied polymer and being designed and constructed to supply said different liquefied polymer to a respective atomizer.

15. The system, method or electrospun structure of claim 14, wherein each atomizer comprises a plurality of spinnerets.

16. The system, method or electrospun structure of claim 14, wherein said plurality of manifolds are mounted on a turret, operable to assume a plurality of orientations, such that at each orientation of said plurality of orientations, a different atomizer is directed to said precipitation electrode.

17. The system, method or electrospun structure of claim 8, wherein the system further comprises at least one pressure sensor operatively associated with said dispenser and being in communication with said data processor, for measuring the hydrostatic pressure of said liquefied polymer in said dispenser.

18. The system, method or electrospun structure of claim 8, wherein the system further comprises at least one temperature sensor operatively associated with said dispenser and being in communication with said data processor, for measuring the temperature of said liquefied polymer in said dispenser.

19. The system, method or electrospun structure of claim 17, wherein the system further comprises a pump system controllable by said data processor, wherein said data processor is configured to stabilize said hydrostatic pressure of said liquefied polymer in said dispenser by controlling said pump system.

20. The system, method or electrospun structure of claim 8, wherein at least one of said dispenser and said precipitation electrode is operable to rotate such that a relative rotary motion is established between said dispenser and said precipitation electrode.

21. The system, method or electrospun structure of claim 20, wherein at least one of said dispenser and said precipitation electrode is operable to move such that a relative linear motion is established between said dispenser and said precipitation electrode.

22. The system, method or electrospun structure of claim 21, wherein said data processor is configured to vary at least one of said relative rotary motion and said relative linear motion so as to control precipitation rate of said polymer fibers on said precipitation electrode.

23. The system, method or electrospun structure of claim 20, wherein said precipitation electrode comprises at least one rotating mandrel.

24. The system, method or electrospun structure of claim 23, wherein said rotating mandrel is operatively associated with a motor controllable by said data processor.

25. The system, method or electrospun structure of claim 1, 2 or 7, wherein said subsidiary electrode system comprises at least one cylindrical electrode.

26. The system, method or electrospun structure of claim 1, 2 or 7, wherein said subsidiary electrode system comprises at least one planar electrode.

27. The system, method or electrospun structure of claim 1, 2 or 7, wherein the system further comprises a first position adjustment mechanism for varying the position of said subsidiary electrode system relative to said precipitation electrode.

28. The system, method or electrospun structure of claim 1, 2 or 7, wherein the system further comprises a second position adjustment mechanism for varying the position of said dispenser relative to said precipitation electrode.

29. The system, method or electrospun structure of claim 1, 2 or 7, wherein the system further comprises an angular adjustment mechanism for varying the relative angle between said dispenser and said precipitation electrode.

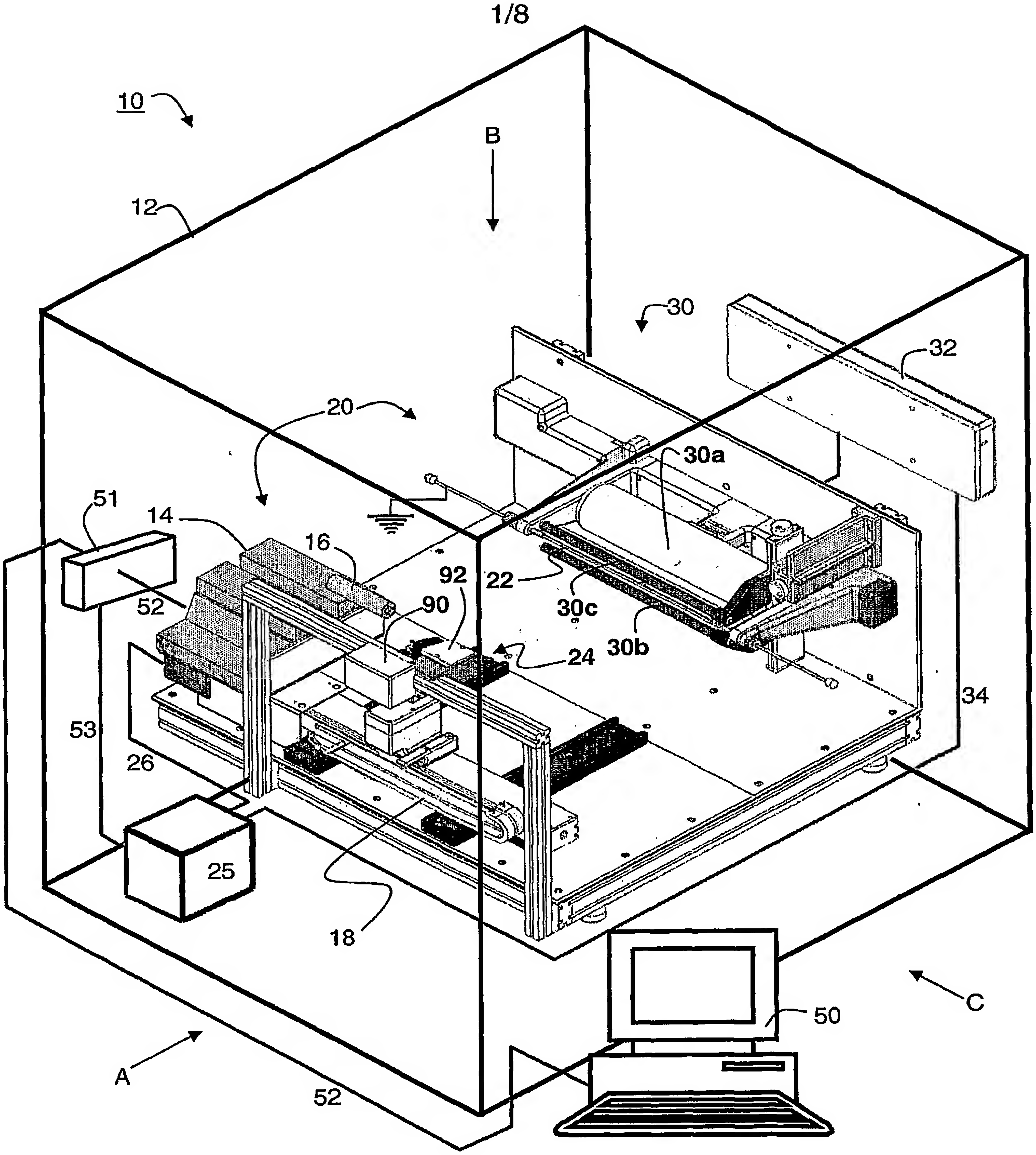
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Fig. 1a

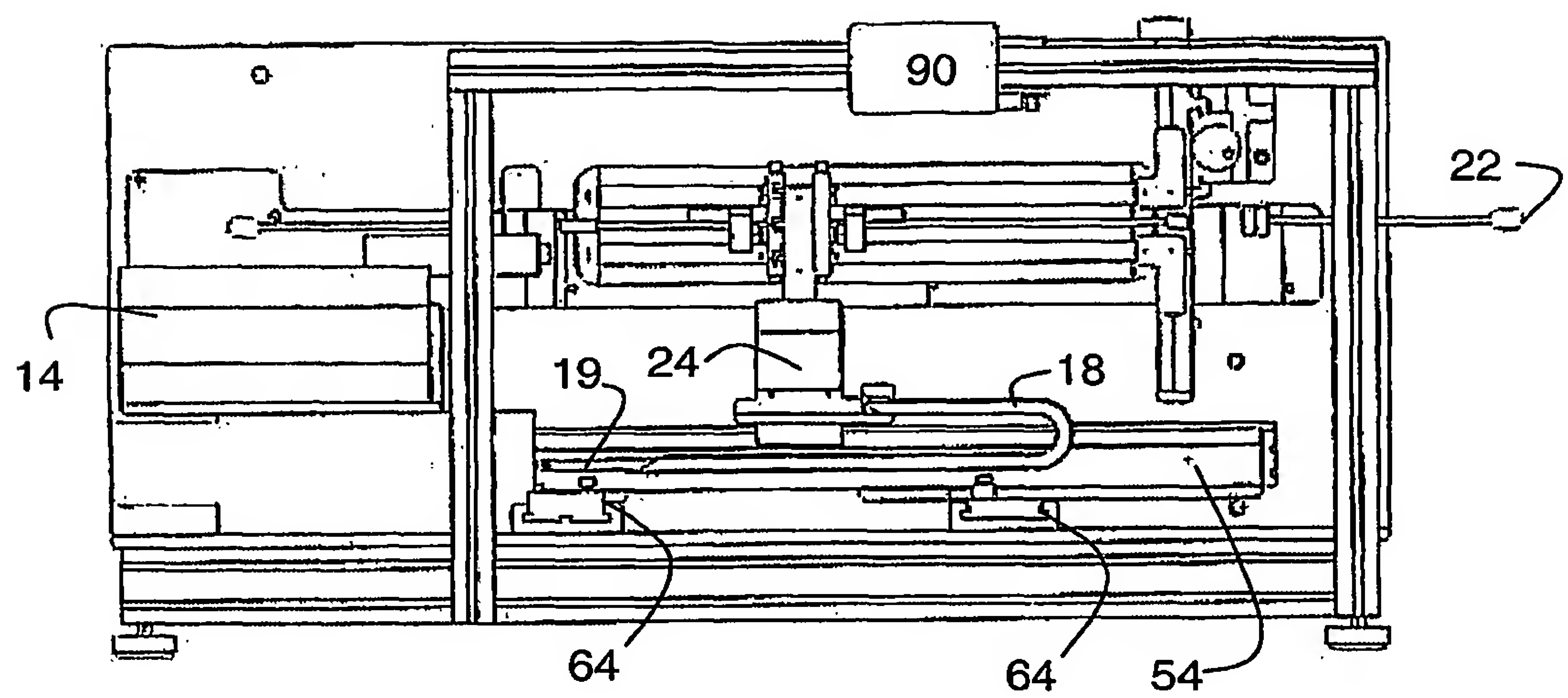


Fig. 1b

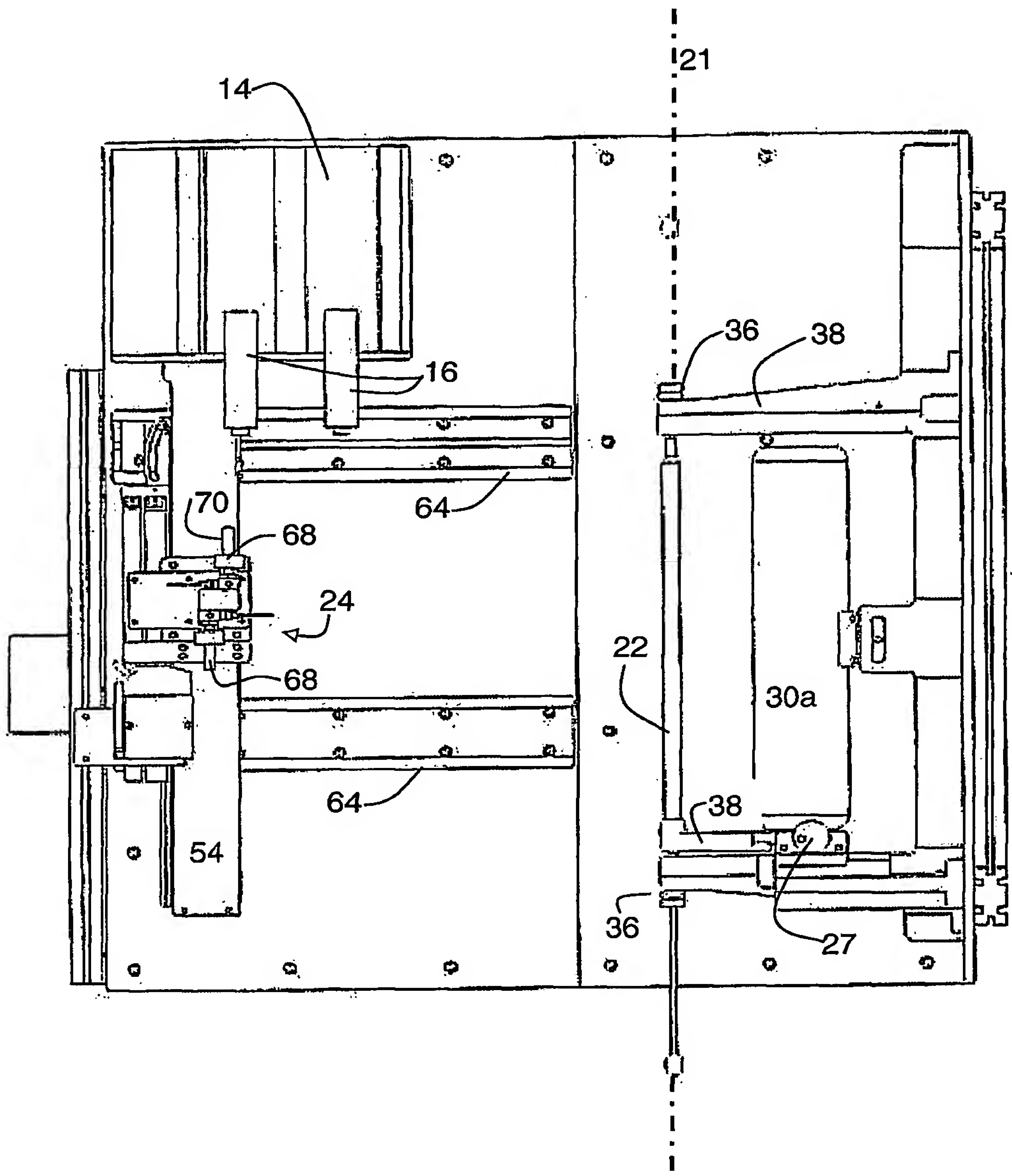


Fig. 1c

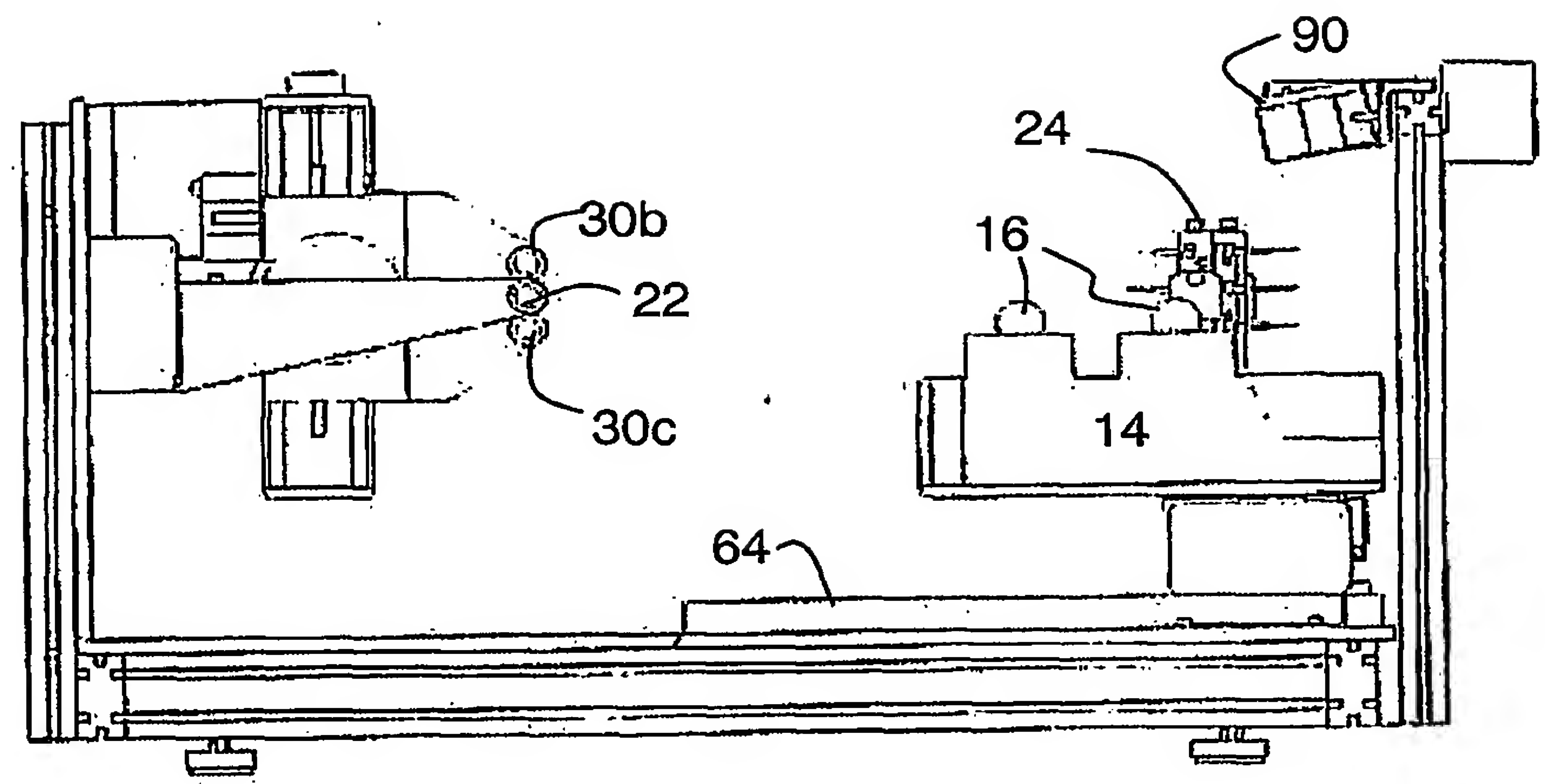


Fig. 1d

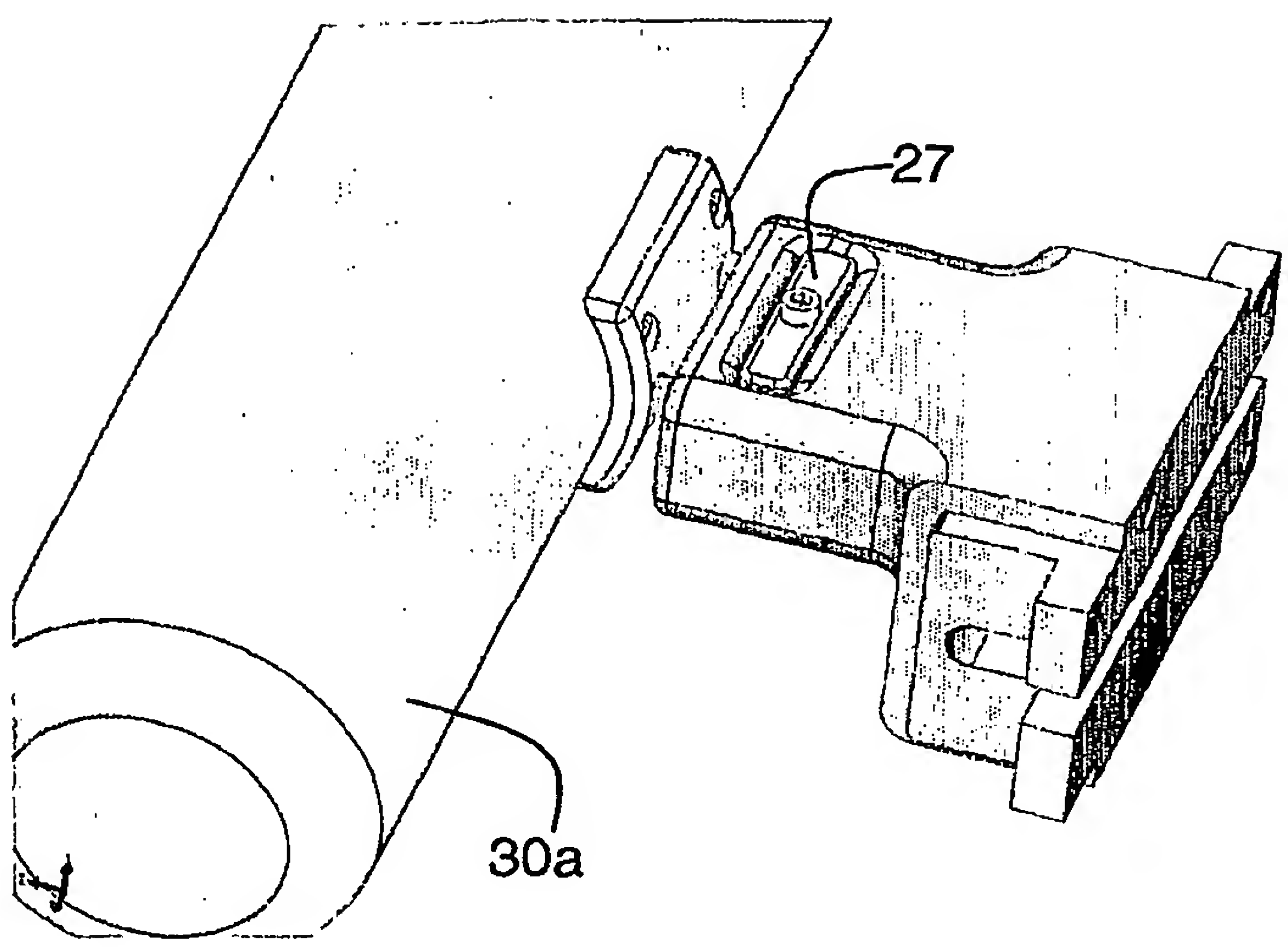


Fig. 2a

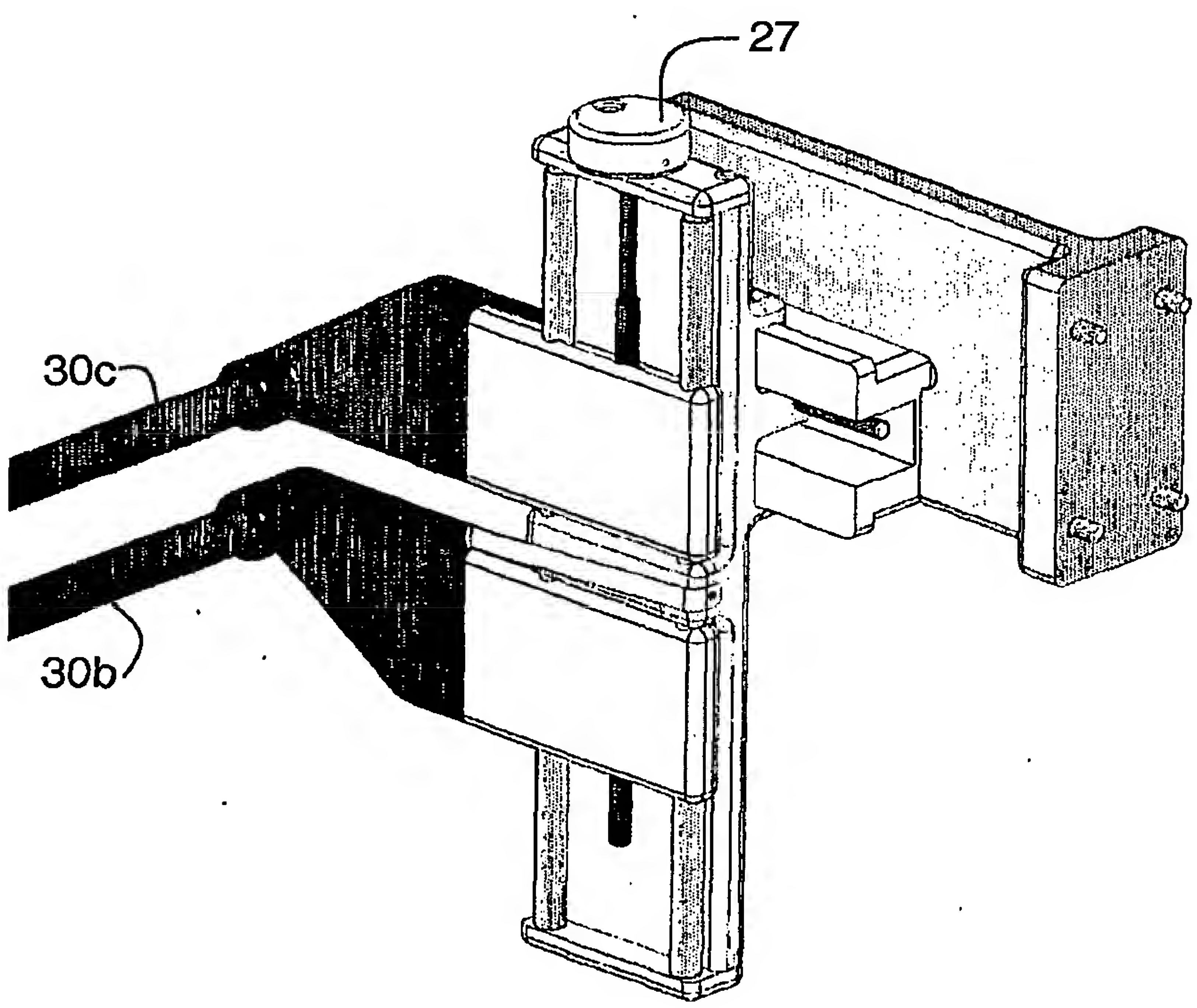


Fig. 2b

Fig. 3

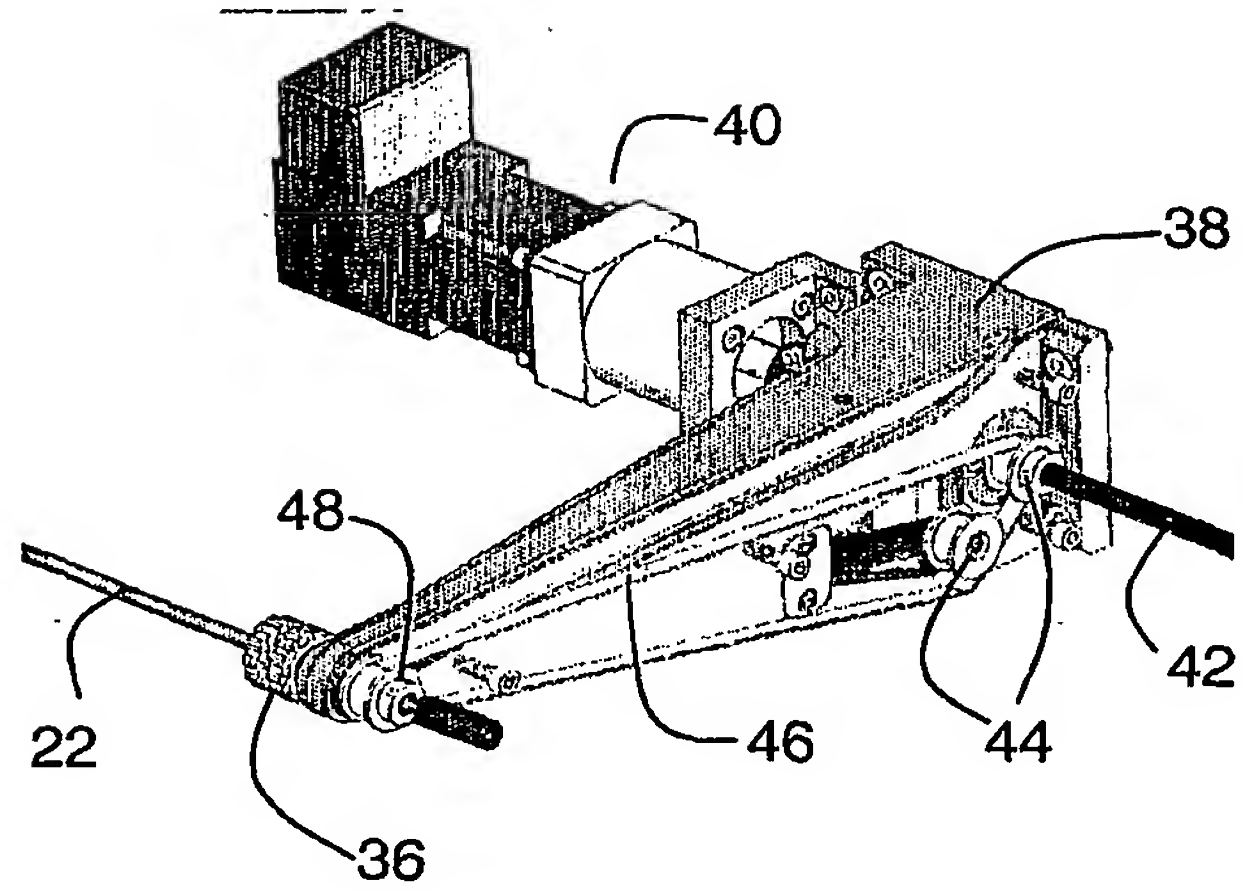


Fig. 4a

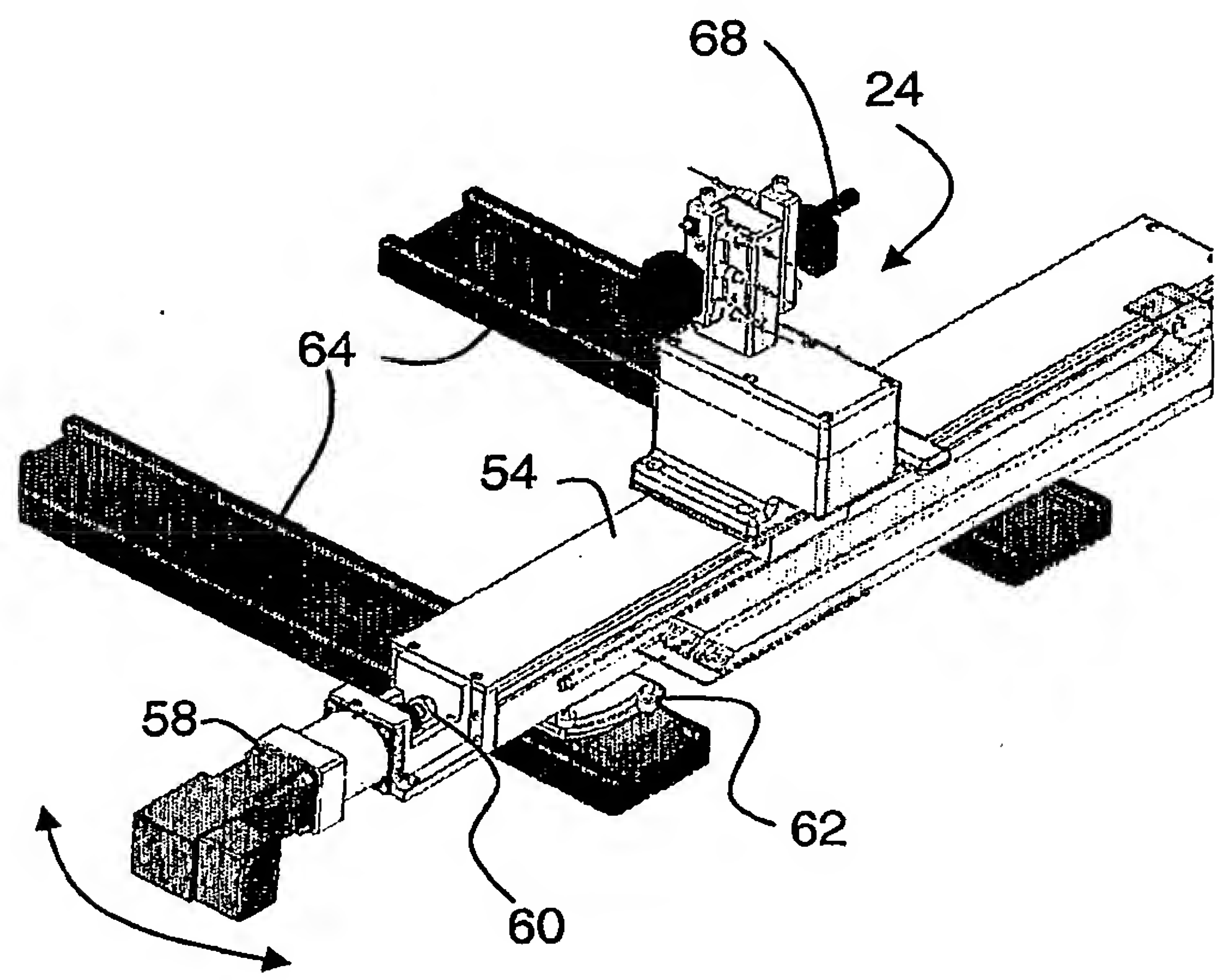
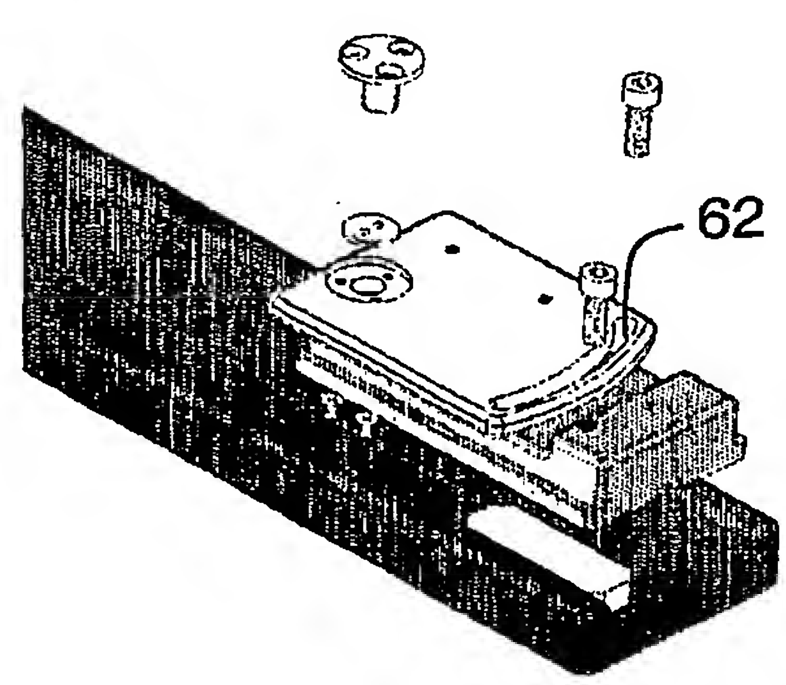


Fig. 4b



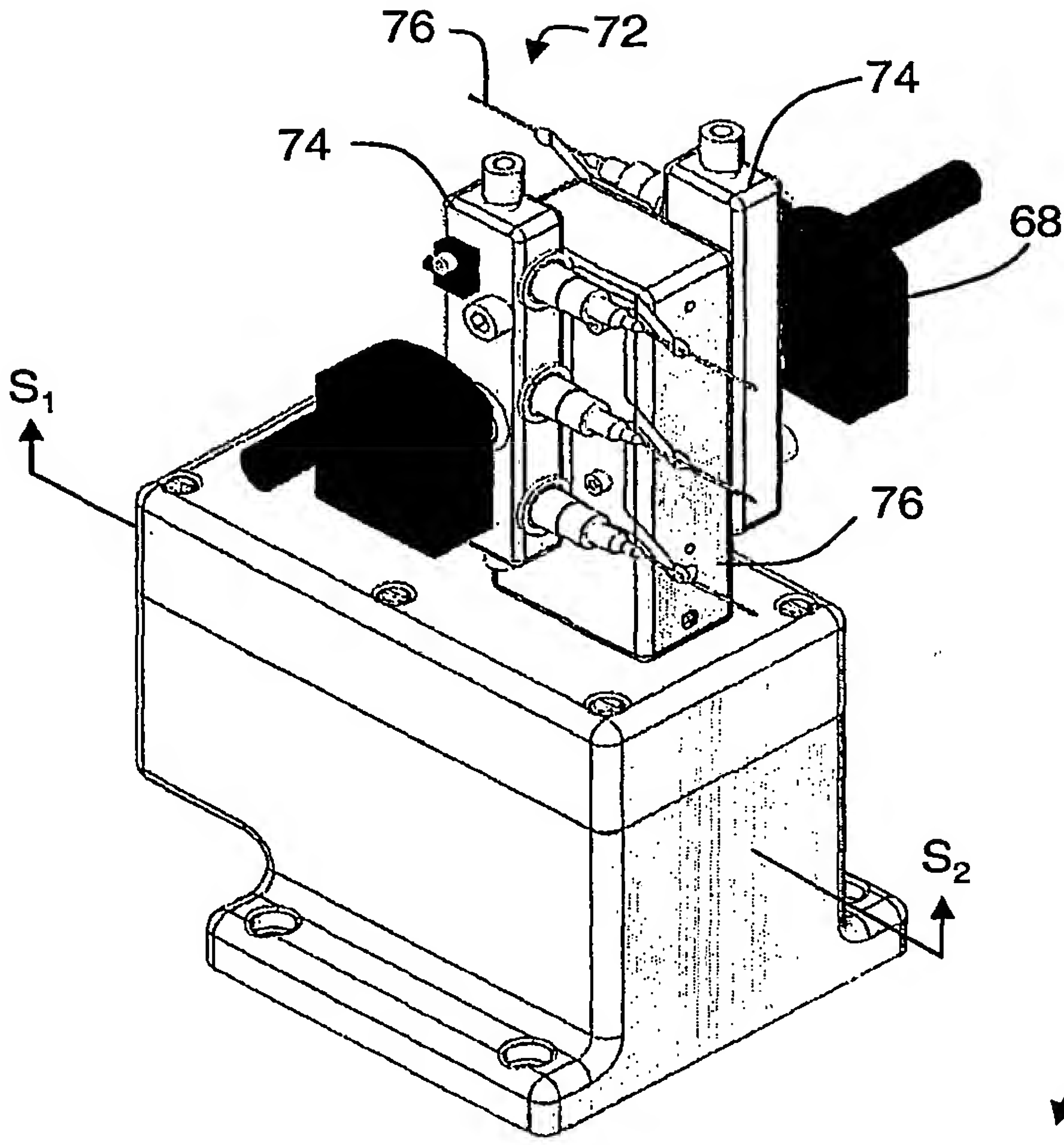


Fig. 5a

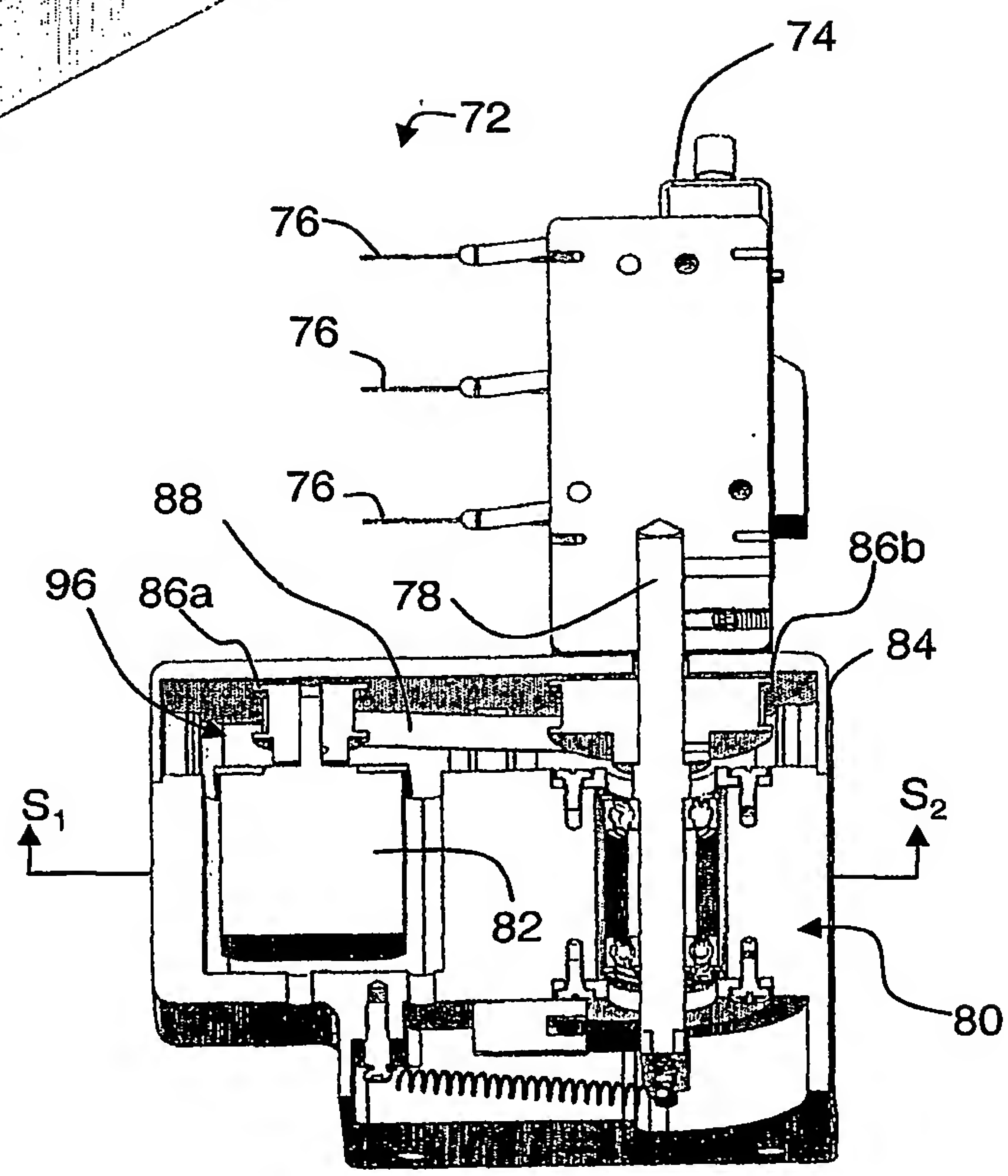


Fig. 5b

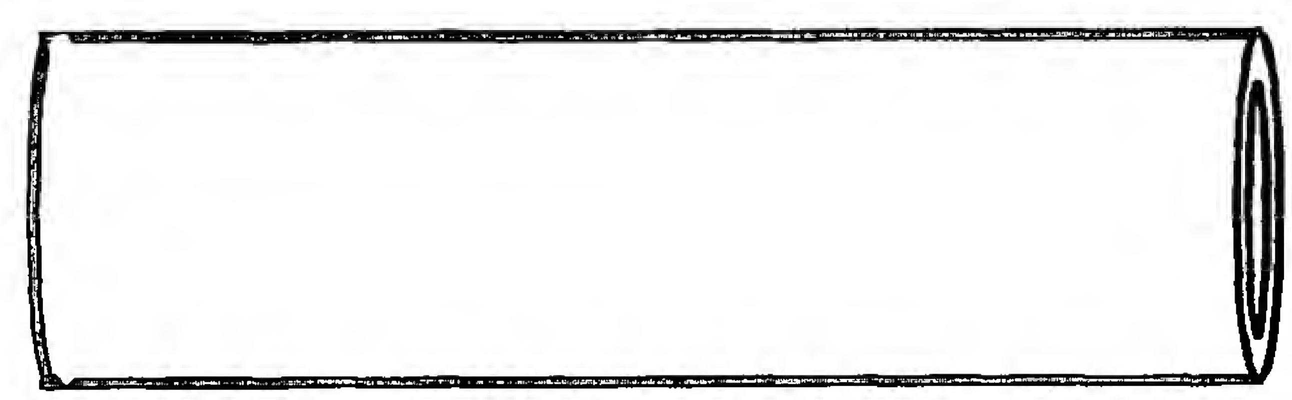


Fig. 6